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Cholinergic nociceptive mechanisms in rat meninges and trigeminal Ganglia: Potential implications for migraine pain

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Abstract

© 2017 Shelukhina, Mikhailov, Abushik, Nurullin, Nikolsky and Giniatullin. Background: Parasympathetic innervation of meninges and ability of carbachol, acetylcholine (ACh) receptor (AChR) agonist, to induce headaches suggests contribution of cholinergic mechanisms to primary headaches. However, neurochemical mechanisms of cholinergic regulation of peripheral nociception in meninges, origin place for headache, are almost unknown. Methods: Using electrophysiology, calcium imaging, immunohistochemistry, and staining of meningeal mast cells, we studied effects of cholinergic agents on peripheral nociception in rat hemiskulls and isolated trigeminal neurons. Results: Both ACh and carbachol significantly increased nociceptive firing in peripheral terminals of meningeal trigeminal nerves recorded by local suction electrode. Strong nociceptive firing was also induced by nicotine, implying essential role of nicotinic AChRs in control of excitability of trigeminal nerve endings. Nociceptive firing induced by carbachol was reduced by muscarinic antagonist atropine, whereas the action of nicotine was prevented by the nicotinic blocker d-tubocurarine but was insensitive to the TRPA1 antagonist HC-300033. Carbachol but not nicotine induced massive degranulation of meningeal mast cells known to release multiple pro-nociceptive mediators. Enzymes terminating ACh action, acetylcholinesterase (AChE) and butyrylcholinesterase, were revealed in perivascular meningeal nerves. The inhibitor of AChE neostigmine did not change the firing per se but induced nociceptive activity, sensitive to d-tubocurarine, after pretreatment of meninges with the migraine mediator CGRP. This observation suggested the pro-nociceptive action of endogenous ACh in meninges. Both nicotine and carbachol induced intracellular Ca 2+ transients in trigeminal neurons partially overlapping with expression of capsaicin-sensitive TRPV1 receptors. Conclusion: Trigeminal nerve terminals in meninges, as well as dural mast cells and trigeminal ganglion neurons express a repertoire of pro-nociceptive nicotinic and muscarinic AChRs, which could be activated by the ACh released from parasympathetic nerves. These receptors represent a potential target for novel therapeutic interventions in trigeminal pain and probably in migraine.

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Keywords

Acetylcholine, Acetylcholine receptor, Mast cells, Meninges, Migraine, Nicotine, Sensory neurons

References

[1] Messlinger K. Migraine: where and how does the pain originate? Exp Brain Res (2009) 196(1):179-93. doi:10.1007/s00221-009-1756-y

[2] Zhang Y, Zhao S, Rodriguez E, Takatoh J, Han BX, Zhou X, et al. Identifying local and descending inputs for primary sensory neurons. J Clin Invest (2015) 125(10):3782-94. doi:10.1172/JCI81156

[3] Goadsby PJ, Charbit AR, Andreou AP, Akerman S, Holland PR. Neurobiology of migraine. Neuroscience (2009) 161(2):327-41. doi:10.1016/j.neuroscience.2009.03.019

[4] Andreou AP, Holland PR, Lasalandra MP, Goadsby PJ. Modulation of nociceptive dural input to the trigeminocervical complex through GluK1 kainate receptors. Pain (2015) 156(3):439-50. doi:10.1097/01.j.pain.0000460325.25762.c0

[5] Ebersberger A, Takac H, Richter F, Schaible HG. Effect of sympathetic and parasympathetic mediators on the release of calcitonin gene-related peptide and prostaglandin E from rat dura mater, in vitro. Cephalalgia (2006) 26(3):282-9. doi:10.1111/j.1468-2982.2005.01035.x

[6] Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med (2002) 8(2):136-42. doi:10.1038/nm0202-136

[7] Yarnitsky D, Goor-Aryeh I, Bajwa ZH, Ransil BI, Cutrer FM, Sottile A, et al. 2003 Wolff Award: possible parasympathetic contributions to peripheral and central sensitization during migraine. Headache (2003) 43(7):704-14. doi:10.1046/j.1526-4610.2003.03127.x

[8] Delepine L, Aubineau P. Plasma protein extravasation induced in the rat dura mater by stimulation of the parasympathetic sphenopalatine ganglion. Exp Neurol (1997) 147(2):389-400. doi:10.1006/exnr.1997.6614

[9] Cady R, Saper J, Dexter K, Manley HR. A double-blind, placebo-controlled study of repetitive transnasal sphenopalatine ganglion blockade with tx360((R)) as acute treatment for chronic migraine. Headache (2015) 55(1):101-16. doi:10.1111/head.12458

[10] Schytz HW, Wienecke T, Olesen J, Ashina M. Carbachol induces headache, but not migraine-like attacks, in patients with migraine without aura. Cephalalgia (2010) 30(3):337-45. doi:10.1111/j.1468-2982.2009.01929.x

[11] Grande G, Nilsson E, Edvinsson L. Comparison of responses to vasoactive drugs in human and rat cerebral arteries using myography and pressurized cerebral artery method. Cephalalgia (2013) 33(3):152-9. doi:10.1177/0333102412468340

[12] Mangione AS, Obara I, Maiaru M, Geranton SM, Tassorelli C, Ferrari E, et al. Nonparalytic botulinum molecules for the control of pain. Pain (2016) 157(5):1045-55. doi:10.1097/j.pain.0000000000000478

[13] Le H, Tfelt-Hansen P, Skytthe A, Kyvik KO, Olesen J. Association between migraine, lifestyle and socioeconomic factors: a population-based cross-sectional study. J Headache Pain (2011) 12(2):157-72. doi:10.1007/s10194-011-0321-9

[14] Dineley KT, Pandya AA, Yakel JL. Nicotinic ACh receptors as therapeutic targets in CNS disorders. Trends Pharmacol Sci (2015) 36(2):96-108. doi:10.1016/j.tips.2014.12.002

[15] Marubio LM, del Mar Arroyo-Jimenez M, Cordero-Erausquin M, Lena C, Le Novere N, de Kerchove d'Exaerde A, et al. Reduced antinociception in mice lacking neuronal nicotinic receptor subunits. Nature (1999) 398(6730):805-10. doi:10.1038/19756

[16] Yamamoto A, Kiguchi N, Kobayashi Y, Maeda T, Ueno K, Yamamoto C, et al. Pharmacological relationship between nicotinic and opioid systems in analgesia and corticosterone elevation. Life Sci (2011) 89(25-26):95--61. doi:10.1016/j.lfs.2011.10.004

[17] Tripathi HL, Martin BR, Aceto MD. Nicotine-induced antinociception in rats and mice: correlation with nicotine brain levels. J Pharmacol Exp Ther (1982) 221(1):91-6

[18] Talavera K, Gees M, Karashima Y, Meseguer VM, Vanoirbeek JA, Damann N, et al. Nicotine activates the chemosensory cation channel TRPA1. Nat Neurosci (2009) 12(10):1293-9. doi:10.1038/nn.2379

[19] Schreiner BS, Lehmann R, Thiel U, Ziemba PM, Beltran LR, Sherkheli MA, et al. Direct action and modulating effect of (+)-and (-)-nicotine on ion channels expressed in trigeminal sensory neurons. Eur J Pharmacol (2014) 728:48-58. doi:10.1016/j.ejphar.2014.01.060

[20] Olesen J, Burstein R, Ashina M, Tfelt-Hansen P. Origin of pain in migraine: evidence for peripheral sensitisation. Lancet Neurol (2009) 8(7):679-90. doi:10.1016/S1474-4422(09)70090-0

[21] Rozniecki JJ, Dimitriadou V, Lambracht-Hall M, Pang X, Theoharides TC. Morphological and functional demonstration of rat dura mater mast cell-neuron interactions in vitro and in vivo. Brain Res (1999) 849(1-2):--15. doi:10.1016/S0006-8993(99)01855-7

[22] Levy D, Burstein R, Kainz V, Jakubowski M, Strassman AM. Mast cell degranulation activates a pain pathway underlying migraine headache. Pain (2007) 130(1-2):166-76. doi:10.1016/j.pain.2007.03.012

[23] Shatillo A, Koroleva K, Giniatullina R, Naumenko N, Slastnikova AA, Aliev RR, et al. Cortical spreading depression induces oxidative stress in the trigeminal nociceptive system. Neuroscience (2013) 253:341-9. doi:10.1016/j.neuroscience.2013.09.002

[24] Schwenger N, Dux M, de Col R, Carr R, Messlinger K. Interaction of calcitonin gene-related peptide, nitric oxide and histamine release in neurogenic blood flow and afferent activation in the rat cranial dura mater. Cephalalgia (2007) 27(6):481-91. doi:10.1111/j.1468-2982.2007.01321.x

[25] Schueler M, Messlinger K, Dux M, Neuhuber WL, De Col R. Extracranial projections of meningeal afferents and their impact on meningeal nociception and headache. Pain (2013) 154(9):1622-31. doi:10.1016/j.pain.2013.04.040

[26] Pedersen SH, Ramachandran R, Amrutkar DV, Petersen S, Olesen J, Jansen-Olesen I. Mechanisms of glyceryl trinitrate provoked mast cell degranulation. Cephalalgia (2015) 35(14):1287-97. doi:10.1177/0333102415574846

[27] Boes T, Levy D. Influence of sex, estrous cycle, and estrogen on intracranial dural mast cells. Cephalalgia (2012) 32(12):924-31. doi:10.1177/0333102412454947

[28] Malin SA, Davis BM, Molliver DC. Production of dissociated sensory neuron cultures and considerations for their use in studying neuronal function and plasticity. Nat Protoc (2007) 2(1):152-60. doi:10.1038/nprot.2006.461

[29] Parker MJ, Beck A, Luetje CW. Neuronal nicotinic receptor beta2 and beta4 subunits confer large differences in agonist binding affinity. Mol Pharmacol (1998) 54(6):1132-9

[30] Bolchi C, Valoti E, Binda M, Fasoli F, Ferrara R, Fumagalli L, et al. Design, synthesis and binding affinity of acetylcholine carbamoyl analogues. Bioorg Med Chem Lett (2013) 23(23):6481-5. doi:10.1016/j.bmcl.2013.09.023

[31] Garcia RC, Dati LM, Torres LH, da Silva MA, Udo MS, Abdalla FM, et al. M1 and M3 muscarinic receptors may play a role in the neurotoxicity of anhydroecgonine methyl ester, a cocaine pyrolysis product. Sci Rep (2015) 5:17555. doi:10.1038/srep17555

[32] Xiao Y, Meyer EL, Thompson JM, Surin A, Wroblewski J, Kellar KJ. Rat alpha3/beta4 subtype of neuronal nicotinic acetylcholine receptor stably expressed in a transfected cell line: pharmacology of ligand binding and function. Mol Pharmacol (1998) 54(2):322-33

[33] Rau KK, Johnson RD, Cooper BY. Nicotinic AChR in subclassified capsaicin-sensitive and-insensitive nociceptors of the rat DRG. J Neurophysiol (2005) 93(3):1358-71. doi:10.1152/jn.00591.2004

[34] Shelukhina I, Paddenberg R, Kummer W, Tsetlin V. Functional expression and axonal transport of alpha7 nAChRs by peptidergic nociceptors of rat dorsal root ganglion. Brain Struct Funct (2015) 220(4):1885-99. doi:10.1007/s00429-014-0762-4

[35] Liu L, Pugh W, Ma H, Simon SA. Identification of acetylcholine receptors in adult rat trigeminal ganglion neurons. Brain Res (1993) 617(1):37-42. doi:10.1016/0006-8993(93)90609-Q

[36] Alimohammadi H, Silver WL. Evidence for nicotinic acetylcholine receptors on nasal trigeminal nerve endings of the rat. Chem Senses (2000) 25(1):61-6. doi:10.1093/chemse/25.1.61

[37] Genzen JR, McGehee DS. Short-and long-term enhancement of excitatory transmission in the spinal cord dorsal horn by nicotinic acetylcholine receptors. Proc Natl Acad Sci U S A (2003) 100(11):6807-12. doi:10.1073/pnas.1131709100 1131709100

[38] Kohlmeier KA, Soja PJ, Kristensen MP. Disparate cholinergic currents in rat principal trigeminal sensory nucleus neurons mediated by M1 and M2 receptors: a possible mechanism for selective gating of afferent sensory neurotransmission. Eur J Neurosci (2006) 23(12):3245-58. doi:10.1111/j.1460-9568.2006.04875.x

[39] Chen SR, Chen H, Yuan WX, Wess J, Pan HL. Differential regulation of primary afferent input to spinal cord by muscarinic receptor subtypes delineated using knockout mice. J Biol Chem (2014) 289(20):14321-30. doi:10.1074/jbc.M114.550384

[40] Dussor GO, Helesic G, Hargreaves KM, Flores CM. Cholinergic modulation of nociceptive responses in vivo and neuropeptide release in vitro at the level of the primary sensory neuron. Pain (2004) 107(1-2):22-32. doi:10.1016/j.pain.2003.09.022

[41] Kilinc E, Guerrero-Toro C, Zakharov A, Vitale C, Gubert-Olive M, Koroleva K, et al. Serotonergic mechanisms of trigeminal meningeal nociception: implications for migraine pain. Neuropharmacology (2016) 116:160-73. doi:10.1016/j.neuropharm.2016.12.024

[42] Simonetti M, Fabbro A, D'Arco M, Zweyer M, Nistri A, Giniatullin R, et al. Comparison of P2X and TRPV1 receptors in ganglia or primary culture of trigeminal neurons and their modulation by NGF or serotonin. Mol Pain (2006) 2:11. doi:10.1186/1744-8069-2-11

[43] Zakharov A, Vitale C, Kilinc E, Koroleva K, Fayuk D, Shelukhina I, et al. Hunting for origins of migraine pain: cluster analysis of spontaneous and capsaicin-induced firing in meningeal trigeminal nerve fibers. Front Cell Neurosci (2015) 9:287. doi:10.3389/fncel.2015.00287

[44] Marszalek JR, Williamson TL, Lee MK, Xu Z, Hoffman PN, Becher MW, et al. Neurofilament subunit NF-H modulates axonal diameter by selectively slowing neurofilament transport. J Cell Biol (1996) 135(3):711-24. doi:10.1083/jcb.135.3.711

[45] Artico M, Cavallotti C. Catecholaminergic and acetylcholine esterase containing nerves of cranial and spinal dura mater in humans and rodents. Microsc Res Tech (2001) 53(3):212-20. doi:10.1002/jemt.1085

[46] Vilotti S, Vana N, Van den Maagdenberg AM, Nistri A. Expression and function of calcitonin gene-related peptide (CGRP) receptors in trigeminal ganglia of R192Q Cacna1a knock-in mice. Neurosci Lett (2016) 620:104-10. doi:10.1016/j.neulet.2016.03.046

[47] Zhang XL, Albers KM, Gold MS. Inflammation-induced increase in nicotinic acetylcholine receptor current in cutaneous nociceptive DRG neurons from the adult rat. Neuroscience (2015) 284:483-99. doi:10.1016/j.neuroscience.2014.10.018

[48] Steen KH, Reeh PW. Actions of cholinergic agonists and antagonists on sensory nerve endings in rat skin, in vitro. J Neurophysiol (1993) 70(1):397-405

[49] Bernardini N, Sauer SK, Haberberger R, Fischer MJ, Reeh PW. Excitatory nicotinic and desensitizing muscarinic (M2) effects on C-nociceptors in isolated rat skin. J Neurosci (2001) 21(9):3295-302

[50] Sekizawa SI, Tsubone H. Nasal receptors responding to noxious chemical irritants. Respir Physiol (1994) 96(1):37-48. doi:10.1016/0034-5687(94)90104-X

[51] Sucher NJ, Cheng TP, Lipton SA. Neural nicotinic acetylcholine responses in sensory neurons from postnatal rat. Brain Res (1990) 533(2):248-54. doi:10.1016/0006-8993(90)91346-I

[52] Genzen JR, Van Cleve W, McGehee DS. Dorsal root ganglion neurons express multiple nicotinic acetylcholine receptor subtypes. J Neurophysiol (2001) 86(4):1773-82

[53] Keiger CJ, Walker JC. Individual variation in the expression profiles of nicotinic receptors in the olfactory bulb and trigeminal ganglion and identification of alpha2, alpha6, alpha9, and beta3 transcripts. Biochem Pharmacol (2000) 59(3):233-40. doi:10.1016/S0006-2952(99)00326-3

[54] Albers KM, Zhang XL, Diges CM, Schwartz ES, Yang CI, Davis BM, et al. Artemin growth factor increases nicotinic cholinergic receptor subunit expression and activity in nociceptive sensory neurons. Mol Pain (2014) 10:31. doi:10.1186/1744-8069-10-31

[55] Smith NJ, Hone AJ, Memon T, Bossi S, Smith TE, McIntosh JM, et al. Comparative functional expression of nAChR subtypes in rodent DRG neurons. Front Cell Neurosci (2013) 7:225. doi:10.3389/fncel.2013.00225

[56] Cao XH, Byun HS, Chen SR, Pan HL. Diabetic neuropathy enhances voltage-activated Ca channel activity and its control by M4 muscarinic receptors in primary sensory neurons. J Neurochem (2011) 119(3):594-603. doi:10.1111/j.1471-4159.2011.07456.x

[57] Nandigama R, Bonitz M, Papadakis T, Schwantes U, Bschleipfer T, Kummer W. Muscarinic acetylcholine receptor subtypes expressed by mouse bladder afferent neurons. Neuroscience (2010) 168(3):842-50. doi:10.1016/j.neuroscience.2010.04.012

[58] Li DP, Chen SR, Pan YZ, Levey AI, Pan HL. Role of presynaptic muscarinic and GABA(B) receptors in spinal glutamate release and cholinergic analgesia in rats. J Physiol (2002) 543(Pt 3):807-18. doi:10.1113/jphysiol.2002.020644

[59] Strassman AM, Weissner W, Williams M, Ali S, Levy D. Axon diameters and intradural trajectories of the dural innervation in the rat. J Comp Neurol (2004) 473(3):364-76. doi:10.1002/cne.20106

[60] Theoharides TC, Donelan J, Kandere-Grzybowska K, Konstantinidou A. The role of mast cells in migraine pathophysiology. Brain Res Brain Res Rev (2005) 49(1):65-76. doi:10.1016/j.brainresrev.2004.11.006

[61] Levy D. Migraine pain, meningeal inflammation, and mast cells. Curr Pain Headache Rep (2009) 13(3):237-40. doi:10.1007/s11916-009-0040-y

[62] Smith JH, Butterfield JH, Cutrer FM. Primary headache syndromes in systemic mastocytosis. Cephalalgia (2011) 31(15):1522-31. doi:10.1177/0333102411421683

[63] Levy D, Kainz V, Burstein R, Strassman AM. Mast cell degranulation distinctly activates trigemino-cervical and lumbosacral pain pathways and elicits widespread tactile pain hypersensitivity. Brain Behav Immun (2012) 26(2):311-7. doi:10.1016/j.bbi.2011.09.016

[64] Munoz-Cruz S, Mendoza-Rodriguez Y, Nava-Castro KE, Yepez-Mulia L, Morales-Montor J. Gender-related effects of sex steroids on histamine release and FcepsilonRI expression in rat peritoneal mast cells. J Immunol Res (2015) 2015:351829. doi:10.1155/2015/351829

[65] Durham PL, Russo AF. Stimulation of the calcitonin gene-related peptide enhancer by mitogen-activated protein kinases and repression by an antimigraine drug in trigeminal ganglia neurons. J Neurosci (2003) 23(3):807-15

[66] Giniatullin R, Di Angelantonio S, Marchetti C, Sokolova E, Khiroug L, Nistri A. Calcitonin gene-related peptide rapidly downregulates nicotinic receptor function and slowly raises intracellular Ca in rat chromaffin cells in vitro. J Neurosci (1999) 19(8):2945-53

[67] Fabbretti E, D'Arco M, Fabbro A, Simonetti M, Nistri A, Giniatullin R. Delayed upregulation of ATP P2X3 receptors of trigeminal sensory neurons by calcitonin gene-related peptide. J Neurosci (2006) 26(23):6163-71. doi:10.1523/JNEUROSCI.0647-06.2006